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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO
07/633,452	12/20/90	TULLIS	R P31-8756

EXAMINER
MARTINELL, J

ART UNIT	PAPER NUMBER
1805	10

DATE MAILED: 04/01/92

CATHRYN CAMPBELL
PRETTY, SCHROEDER,
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 01/09/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 40-43, 45-47, 49, and 51-61 are pending in the application.
   Of the above, claims 40-43, 45-47, 49, 51, and 52 are withdrawn from consideration.
2. ☒ Claims 1-39, 44, 48, 50, and 62 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 53-61 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev.9-89)

Claims 40-43, 45-47, 49, 51, and 52 stand withdrawn from furth r consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Election was made without traverse in Paper No. 9.

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

The Information Disclosure Statement filed October 18, 1993 has been considered. The listed references that are crossed off are already of record. Applicants should not list references that are already of record. Additionally, in view of the number and nature of errors on form PTO-1449, applicant's attention is directed to MPEP 609.

The disclosure is objected to because of the following informalities:

> In the amendment filed January 9, 1992, the amendment to the first page of the specification misidentified the oldest parent application as Serial No. 07/314,214. The correct Serial No. is 07/314,124.

Appropriate correction is required.

Claims 64-72 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the preparation of stabilized forms of oligodeoxyribonucleotides that are phosphotriesters. See M.P.E.P. §§ 706.03(n) and 706.03(z). This rejection is repeated for reasons already of record (e.g., Office action mailed April 1, 1992, page 2, third full paragraph). Applicant' arguments (paper no. 15, pages 3-4) and Exhibits A-E submitted with the response filed October 1, 1992 are not convincing. First, Exhibits A, B, and C were published subsequent to the effective filing date of the instant application. Applicant's argument that these articles

ought to b convincing because th y show the level of skill in the art at the time the invention was made is not convincing because of the rapid rate of developments in the field of chemical synthesis of oligodeoxyribonucleotid s in the early 1980s. Because of the rapid rate of development at that time, the level of skill in the art could change rapidly over a period of only a few months. Thus, the citation of articles published in 1982, 1983, and 1984 in order to establish a level of skill in the art of oligodeoxyribonucleotide synthesis in 1981 is not convincing. Second, applicant's arguments and Exhibits A-E are not sufficient to overcome this rejection because none of Exhibits A-E discusses what is crucial to the use of oligodeoxyribonucleotides in this invention. For example, none of the references discusses (a) the ability of the particular oligodeoxyribonucleotides of any of the references to get into cells, (b) the ability of the particular oligodeoxyribonucleotid s of any of the references to hybridize effectively and specifically to a nucleic acid of interest (i.e. a target nucleic acid), or (c) the in vivo stability of any particular oligodeoxyribonucleotides of any of the references. Therefore, given the lack of guidance as to which types of oligodeoxyribonucleotides to use in the instant invention or even the mere mention of potential candidate oligodeoxyribonucleotides to use and the failure of applicant to establish that one of skill in the art would readily know which oligodeoxyribonucleotide to use in the absence of such a disclosure in the instant application, one of skill in the art would be compelled to undertake undue experimentation in order to practice the invention as claimed. Applicant did not argue this rejection in the response filed October 18, 1993. Additionally, the claims embrace the use of oligoribonucleotides, but the instant application do s not teach one of skill in the art how to make or use

oligoribonucleotides. Finally, the instant application provides no data and provides no methods for actually getting short DNAs or RNAs into cells.

Claims 64-72 are rejected under 35 U.S.C. § 103 as being unpatentable over Itakura et al in view of either one of Paterson et al or Hastie et al in further view of either one of Summerton or Miller et al. This rejection is repeated for reasons already of record (e.g., Office action mailed April 1, 1992, page 3). Applicant's argument (paper no. 15, pages 6-7) and Exhibits G-L submitted with the response filed October 1, 1992 are not convincing. Exhibits G-L do not establish that claims not limited to phosphotriesters were present in the parent application at a time when the obviousness rejection that corresponds to this rejection was not made. The record in the parent application indicates that the obviousness rejection that corresponds to this rejection was made as late as the Office action mailed on March 15, 1990 and was maintained in the Advisory action mailed on August 28, 1990. Applicant's arguments (paper no. 24, pages 3-19) are not convincing. Applicant argues that one of ordinary skill in the art would not have expected hybrid arrested translation to occur because the state of the art showed that short oligonucleotides were insufficient to stop translation if the region of hybridization was in the coding region of the mRNA. To support this argument applicant relies on some publications that appeared subsequent to the effective filing date of the instant application (e.g., Blake et al, Biochemistry 24: 6132 (1985), Blake et al, Biochemistry 24: 6139 (1985), and Haeuptle et al, Nucleic Acids Res. 14: 1427 (1986)). The reliance on these documents is most unconvincing becaus one of ordinary skill in the art could not have been steered away from the obviousness of the invention as outlined in the rejection by information that was published later (i.e. after the

effective filing date of the instant application, October 23, 1981). Additionally, nothing in applicant's arguments negates the results reported in both of the secondary references (Paterson et al and Hastie et al). For example, the title and abstract of Paterson et al clearly discloses the fact that hybrid arrested translation occurs when cDNA is hybridized to mRNA in vitro. Likewise, Hastie et al (e.g., Figure 2) shows that cDNA hybridized to mRNA prevents the translation of the mRNA. Thus, at the time the instant invention was made, one of ordinary skill in the art would have known that mRNA hybridized to DNA would not be translated in vitro and would have expected that mRNA in vivo would behave the same way. Knowing that hybrid arrested translation would occur, the determination of the shortest oligonucleotide to effect translation arrest would have been a matter of routine optimization experimentation. Finally, it is noted that Summerton discloses the use of oligonucleotides that crosslink with the complementary strand to inactivate the target sequence(e.g., see page 79, first paragraph under section 2). None of applicant's arguments is directed to the crosslinking of the oligonucleotide and the target sequence.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 at (703) 305-3014. The faxing of such papers must conform with the rules published in the Official Gazette, 1156 OG 61 (November 16, 1993).

Any inquiry concerning this communication should be directed to J. Martinell at telephone number (703) 308-0296.

JAMES MARTINELL, PH.D.
SENIOR LEVEL EXAMINER
GROUP 1800